Data Evaluation Report on the degradation kinetics of fenamidone in aerobic soil

PMRA Submission Number {.....} EPA MRID Number 45930001

Data Requirement: PMRA Data Code:
EPA DP Barcode:
OECD Data Point:
EPA Guideline: Non-Guideline (kinetics modeling of aerobic soil metabolism)

Test material:
Common name: Fenamidone.
Chemical name
IUPAC name: (+)-(4 S)-4-Methyl-2-methylthio-4-phenyl-(1H)-1-phenylamino-2-imidazolin-5-one.
CAS name: (5 S)-3,5-Dihydro-5-methyl-2-(methylthio)-5-phenyl-3-(phenylamino)- 4H-imidazol-4-one.
CAS No: 161326-34-7.
Synonyms: RPA 407213.
SMILES string:

Primary Reviewer: Dana Worcester
Dynamac Corporation

Signature: Dana Worcester
Date: 8/21/03

QC Reviewer: Kathleen Ferguson
Dynamac Corporation

Signature: Kathleen Ferguson
Date: 8/21/03

Secondary Reviewer: Silvia Termes
EPA

Signature:
Date: 8th. Sept., 2003

Company Code:
Active Code:
Use Site Category:
EPA PC Code: 046679

CITATION: Ramanarayanan, T.S. 2001. Determination of degradation kinetics of fenamidone (RPA 407213) and its metabolites in two soils under aerobic conditions at 20°C according to USEPA guidelines. Unpublished study performed and submitted by Aventis CropScience, Research Triangle Park, NC. Study ID: W01E601. Final report issued May 22, 2001.

EXECUTIVE SUMMARY:

The degradation of (5 S)-3,5-dihydro-5-methyl-2-(methylthio)-5-phenyl-3-(phenylamino)- 4H-imidazol-4-one (fenamidone; RPA 407213) and its transformation product RPA 412636 [(5 S)-5-methyl-5-phenyl-2,4-imidazolidinedione] was studied in MRIDs 45385819 [Burr, C.M., and Bullus, C.M. 2000. [^{14}C]-Fenamidone aerobic soil metabolism.] and MRID 45385820 [Clarke, D.E. 2000. [^{14}C]-RPA 412636: Rate of aerobic degradation in three soil types at 20°C.], respectively. These MRIDs were reviewed in a previous data package. The current report uses the data from those studies and the Thomae Optimized Pharmacokinetics Fitting Program (TopFit 2.0) to estimate half-lives for RPA 413255 [(5 S)-3,5-dihydro-5-methyl-2-(methylthio)-3-[(2-nitrophenyl)amino]-5-phenyl-4H-imidazol-4-one], RPA 411639 [(5 S)-3,5-dihydro-5-methyl-2-(methylthio)-3-[(4-nitrophenyl)amino)]-5-phenyl-4H-imidazol-4-one], RPA 221607 [(5 S)-5-methyl-3-[(4-nitrophenyl)amino]-5-phenyl-2,4-imidazolidinedione], RPA 221701 [(5 S)-5-methyl-3-[(2-nitrophenyl)amino]-5-phenyl-2,4-imidazolidinedinone], and RPA 412708 [(5 S)-3,5-dihydro-5-methyl-2-(methylthio)-5-phenyl-4H-imidazol-4-one]. Because they shared a common mechanism of formation, RPA 413255 and RPA 411639 were analyzed together, as were RPA 221701 and RPA 221607.

In the sandy loam soil, the estimated half-life of RPA 413255 plus RPA 411639 was 79.2 days, of RPA 221701 plus RPA 221607 was 278.0 days, and of RPA 412708 was 4.4 days. In the loam soil, the estimated half-life of RPA 413255 plus RPA 411639 was 173.0 days and of RPA 412708 was 133 days; the half-life of RPA 221701 plus RPA 221607 in the loam soil was not estimated because these compounds were not isolated in significant amounts.

Although half-lives for fenamidone and RPA 412636 were calculated using the TopFit model, the study author stated that the half-lives for these compounds that were determined in MRIDs 45385819 and 45385820, respectively, were more appropriate and applicable for exposure analysis. Using the TopFit model, the half-lives for fenamidone in the sandy loam and loam soils were 6.7 and 9.7 days, respectively. For RPA 412636, the half-lives in the sandy loam and loam soils were reported to be >365 days.

METHODOLOGY:

In MRID 45385819, the degradation of fenamidone, applied at a nominal rate of 1.1 mg a.i./kg soil, was studied in Wisconsin sandy loam soil (pH 4.8, organic carbon 1.2%) and California loam soil (pH 8.2, organic carbon 0.8%) that were maintained under aerobic conditions in darkness at 20 ± 1°C with a soil moisture content of 75% of 0.33 bar for 365 days. In the sandy loam soil, fenamidone dissipated with reviewer-calculated half-lives of 4.8-5.4 days using first-order linear regression analysis (Excel 2000, 0-7 day data). In the loam soil, fenamidone dissipated with a half-life of 8.1 days (0-14 day data). The first order degradation half-lives calculated by the study author were 6.7 days for the sandy loam soil and 9.9 days for the loam soil (MRID 45930001, p.

7). DT50 and DT90 values for fenamidone were calculated by the study author using KIM, a nonlinear three-compartment Schering AG kinetic modeling program. DT50 values were 3.6 and 7.8 days for the sandy loam and loam soils, respectively, and the respective DT90 values were 92 and 82 days. RPA 413255, RPA 411639, RPA 221701, RPA 221607, RPA 412708, and RPA 412636 were identified as transformation products (Note: In MRID 45930001, in was noted that the original code numbers identified for these compounds were for the racemic mixture, but that since only the S-enantiomer exists, the transformation products have been recoded, pp. 9, 10).

In MRID 45385820, the degradation of the fenamidone transformation product RPA 412636, applied at a nominal rate of 0.5 µg a.i./g soil, was studied in a Florida sand soil (pH 7.9, organic carbon 0.7%), a UK clay loam soil (pH 8.5, organic carbon 2.0%), and a Mississippi silt loam soil (pH 7.0, organic carbon 0.3%) for 365 days under aerobic conditions in darkness at 20 ± 1°C with a soil moisture of 75% of 1/3 bar. The reviewer-calculated half-lives (Excel 2000) were 453 days for the sand soil, 105 days for the clay loam soil, and 462 days for the silt loam soil. These individual values were similar to those calculated by the study author, who determined the mean degradation half-life in the three soils was 327 days (MRID 45930001, p. 7).

In this MRID, the Thomae Optimized Pharmacokinetics Fitting Program (TopFit 2.0) was used to estimate half-lives for RPA 413255, RPA 411639, RPA 221701, RPA 221607, and RPA 412708 using the data presented in MRIDs 45385819 and 45385820. TopFit is a curve-fitting program for linear and non-linear compartmental modeling. The proposed kinetic model is presented in Figure 3, p. 23. For the purpose of the model, data from the C-phenyl and N-phenyl labels were combined. Also, because the mechanism of formation was assumed to be similar and to increase the degrees of freedom, RPA 413255 and RPA 411639 were placed together in Compartment 3 and RPA 221701 and RPA 221607 were placed together in Compartment 4 (p. 14; Figure 3, p. 23).

RESULTS:

The results of the TopFit analysis are presented in DER Tables 1 and 2. The study author stated that the calculated half-lives of fenamidone and RPA 412636 should be considered valid only within the scope of the TopFit analysis, and that the half-lives that were determined in MRIDs 45385819 and 45385820 are more appropriate and should be used in exposure calculations (p. 15). The primary purpose of the TopFit analysis was to generate half-lives for transformation products that were not studied independently.

Table 1: Half-life values in sandy loam soil

	Half-life (days)	Regression equation	r^2
Fenamidone	13.4 (6.7)*	$T1/2 = \ln(2)/\sum_{j} k_{i-j}$	0.85
RPA 412708	4.43		0.75
RPA 413255 RPA 411639	79.2		0.95
RPA 221701 RPA 221607	278.0		0.94
RPA 412636	>365 (327)*		0.98

Data obtained from Table 1, p. 18 in the study report.
* Values reported in the original studies.

Table 2: Half-life values in loam soil

	Half-life (days)	Regression equation	r^2
Fenamidone	9.7 (9.9)*	$T1/2 = \ln(2)/\sum_{j} k_{i-j}$	0.98
RPA 412708	133		0.93
RPA 413255 RPA 411639	173.0		0.64
RPA 412636	>365 (327)*		0.93

Data obtained from Table 2, p. 19 in the study report.
* Values reported in the original studies.

REVIEWER'S COMMENTS:

1. The study author noted that the low r^2 value (0.64) for the transformation products RPA 413255 and RPA 411639 may be due to the variability in the degradation study replicate data on day 14 and 56 (p. 15).

2. The nominal application rate of 1.2 kg a.i./ha that was used in the metabolism studies corresponded to the maximum seasonal application rate for fenamidone (p. 9).

3. The study author noted that the original studies utilized racemic forms of fenamidone and its transformation products, along with the S-enantiomer forms (p. 9). However, fenamidone is

produced as an essentially pure S-enantiomer. A supplementary biotransformation study found that fenamidone and its transformation products exist only as the S-enantiomer form (p. 10). Many of the original studies were written utilizing the racemic names and codes, rather than the corresponding S-enantiomer.

4. The study author reported that degradation kinetics assessment was not subject to EPA GLP Standards (p. 3).

REFERENCES:

1. Burr, C.M., and Bullus, C.M. 2000. [^{14}C]-Fenamidone aerobic soil metabolism. Unpublished study performed and submitted by Aventis CropScience, Essex, UK. Laboratory Project ID: 13061. Experimental start date October 22, 1998, and completion date December 13, 1999. Final report issued July 14, 2000.

2. Clarke, D.E. 2000. [^{14}C]-RPA 412636: Rate of aerobic degradation in three soil types at 20°C. Unpublished study performed and submitted by Aventis CropScience, Essex, UK. Laboratory Project ID: 17583. Study experimental start date March 30, 1999, and experimental end data June 12, 2000. Final report issued August 22, 2000.

Attachment 1

Structures of Parent and Transformation Products

RPA 407213

IUPAC name: (*S*)-5-Methyl-2-methylthio-5-phenyl-3-phenylamino-3,5-dihydroimidazol-4-one
(*S*)-4-Methyl-2-methylthio-4-phenyl-1-phenylamino-5(4H)-imidazolone

CAS name: 4*H*-Imidazol-4-one, 3,5-dihydro-5-methyl-2-(methylthio)-5-phenyl-3-(phenylamino)-, (S)-

CAS #: 161326-34-7

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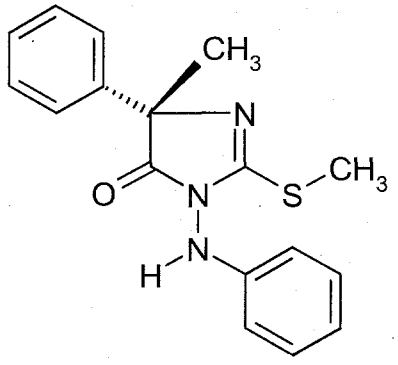

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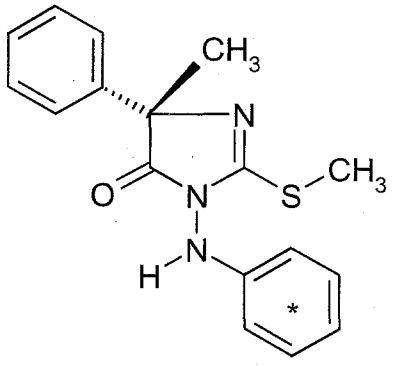
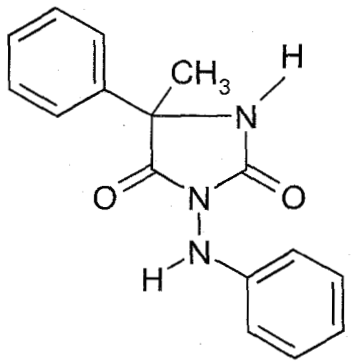


*Position of [^{14}C]-radiolabel.

RPA 405862
IUPAC name: 5-Methyl-5-phenyl-3-phenylaminoimidazolidine-2,4-dione
CAS name: 2,4-Imidazolidinedione, 5-methyl-5-phenyl-3-(phenylamino)-
CAS #: 153969-11-0

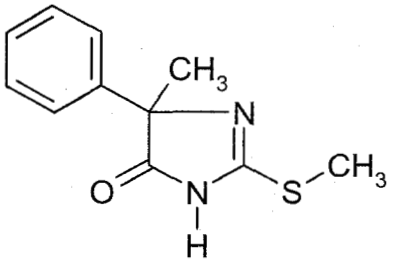


RPA 408056

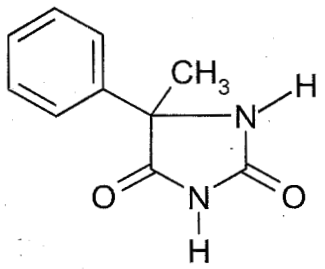
IUPAC name: 5-Methyl-2-methylthio-5-phenyl-3,5-dihydroimidazol-4-one
4-Methyl-2-methylthio-4-phenyl-2-imidazolin-5-one

CAS name: 4*H*-Imidazol-4-one, 3,5-dihydro-5-methyl-2-(methylthio)-5-phenyl-

CAS #: N/A



RPA 717879
IUPAC name: 5-Methyl-5-phenylimidazolidine-2,4-dione
CAS name: 2,4-Imidazolidinedione, 5-methyl-5-phenyl-
CAS #: 6843-49-8

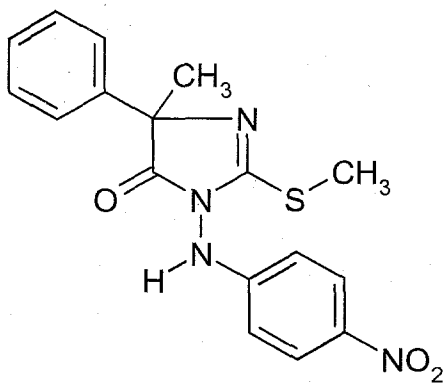


RPA 406012

IUPAC name: 5-Methyl-2-methylthio-3-(4-nitrophenylamino)-5-phenyl-3,5-dihydroimidazol-4-one

CAS name: 4*H*-Imidazol-4-one, 3,5-dihydro-5-methyl-2-(methylthio)-3-[(4-nitrophenyl)amino]-5-phenyl-

CAS #: 151022-56-9
451022-66-9

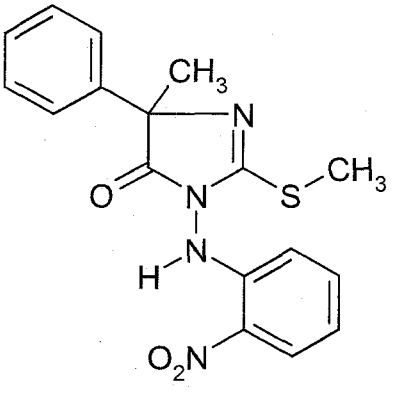


RPA 410914

IUPAC name: 5-Methyl-2-methylthio-3-(2-nitrophenylamino)-5-phenyl-3,5-dihydroimidazol-4-one
(4RS)-4-methyl-2-methylthio-(1H)-1-(2-nitrophenylamino)-4-phenyl-2-imidazolin-5-one

CAS name: 4*H*-Imidazol-4-one, 3,5-dihydro-5-methyl-2-(methylthio)-3-(2-nitrophenylamino)-5-phenyl-

CAS #: N/A

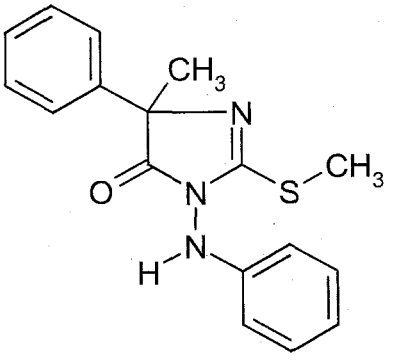


RPA 405803

IUPAC name: 5-Methyl-2-methylthio-5-phenyl-3-phenylamino-3,5-dihydroimidazol-4-one

CAS name: 4*H*-Imidazol-4-one, 3,5-dihydro-5-methyl-2-(methylthio)-5-phenyl-3-(phenylamino)-

CAS #: 151022-37-6



RPA 409446
IUPAC name: 5-Methyl-3-(4-nitrophenylamino)-5-phenylimidazolidine-2,4-dione
CAS name: 2,4-Imidazolidinedione, 5-methyl-3-(4-nitrophenylamino)-5-phenyl-
CAS #: N/A

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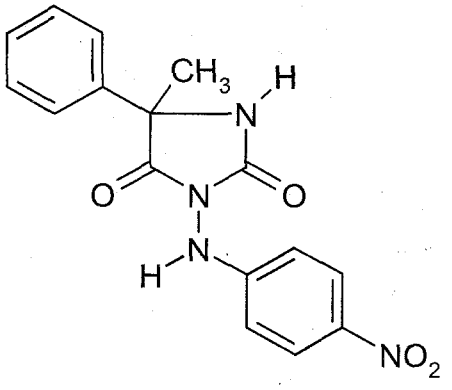

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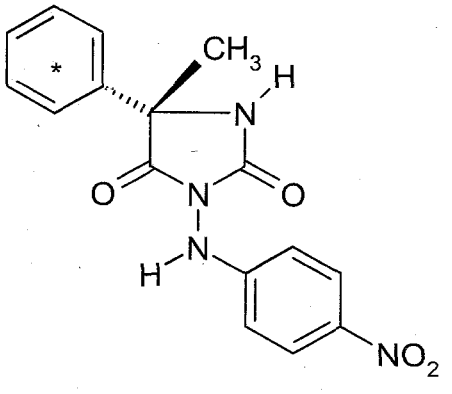


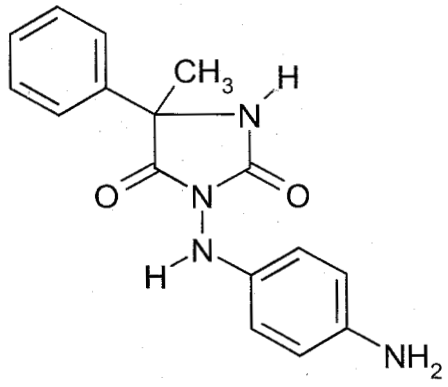
*Position of [^{14}C]-radiolabel.

RPA 409445

IUPAC name: 3-(4-Aminophenylamino)-5-methyl-5-phenylimidazolidine-2,4-dione

CAS name: 2,4-Imidazolidinedione, 3-(4-aminophenylamino)-5-methyl-5-phenyl-

CAS #: N/A

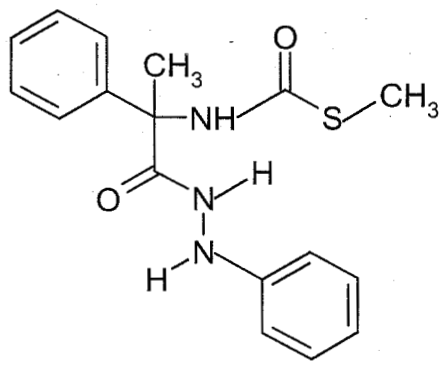


RPA 407599

IUPAC name: [1-Phenyl-1-(N'-phenylhydrazinocarbonyl)-ethyl]-thiocarbamic acid S-methyl ester

CAS name: Benezeneacetic acid, α-methyl-N-thiocarboxy-, S-methyl ester, 2-phenylhydrazide

CAS #: N/A

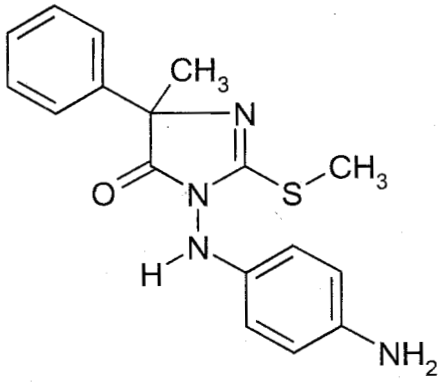


RPA 409352

IUPAC name: 3-(4-Aminophenylamino)-5-methyl-2-methylthio-5-phenyl-3,5-dihydroimidazol-4-one

CAS name: 4*H*-Imidazol-4-one, 3,5-dihydro-3-(4-aminophenylamino)-5-methyl-2-(methylthio)-5-phenyl-

CAS #: N/A

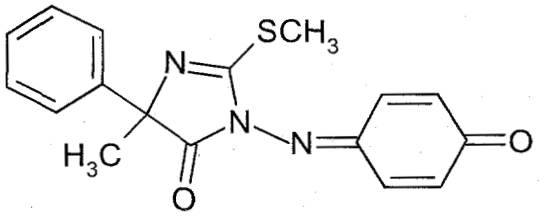


RPA 418915

IUPAC name: (*S*)-5-Methyl-2-methylthio-3-[4-oxo-2,5-cyclohexadien-1-ylidene)amino]-5-phenyl-3,5-dihydroimidazol-4-one

CAS name: N/A

CAS #: N/A

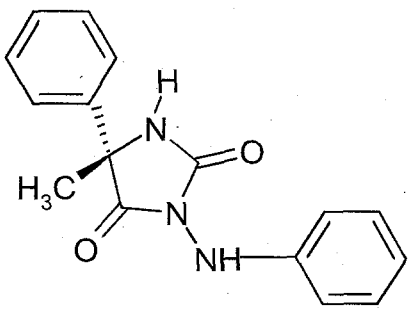


RPA 410193

IUPAC name: (*S*)-4-Methyl-4-phenyl-1-phenylaminoimidazolidin-2,5-dione

CAS name: N/A

CAS #: N/A



RPA 409344

IUPAC name: (R,S)-2-methyl-2-phenyl-N-(phenylazocarbonyl)glycine
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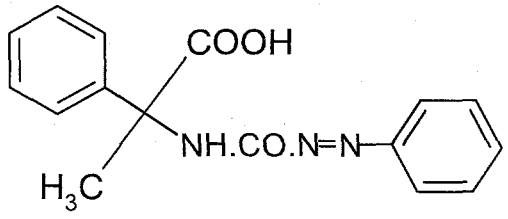
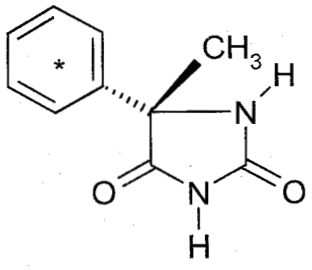
CAS name: N/A

CAS #: N/A



RPA 412636
IUPAC name: (*S*)-5-Methyl-5-phenylimidazolidine-2,4-dione
CAS name: 2,4-Imidazolidinedione,5-methyl-5-phenyl-, (S)
CAS #: 27539-12-4



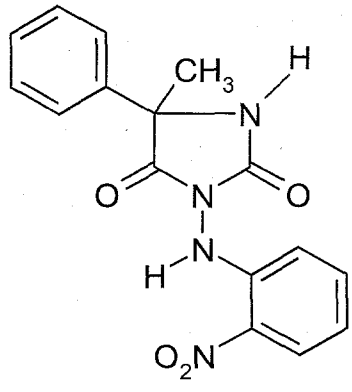
* Position of [^{14}C] radiolabel.

RPA 410995

IUPAC name: 5-Methyl-3-(2-nitrophenylamino)-5-phenylimidazolidine-2,4-dione

CAS name: 2,4-Imidazolidinedione, 5-methyl-3-[(2-nitrophenyl)amino]-5-phenyl-

CAS #: N/A

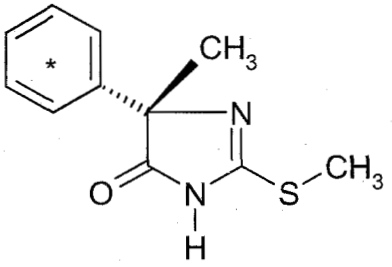


RPA 412708

IUPAC name: (*S*)-5-Methyl-2-methylthio-5-phenyl-3,5-dihydroimidazol-4-one

CAS name: 4*H*-Imidazol-4-one, 3,5-dihydro-5-methyl-2-(methylthio)-5-phenyl-,(S)-

CAS #: N/A

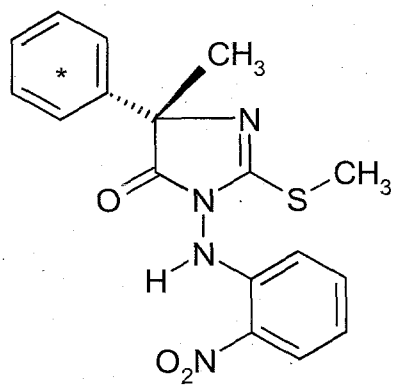


RPA 413255

IUPAC name: (*S*)-5-Methyl-2-methylthio-3-(2-nitrophenylamino)-5-phenyl-3,5-dihydroimidazol-4-one

CAS name: 4*H*-Imidazol-4-one, 3,5-dihydro-5-methyl-2-(methylthio)-3-(2-nitrophenylamino)-5-phenyl-,(S)-

CAS #: N/A



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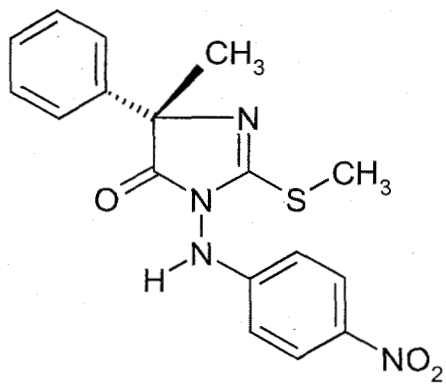
RPA 411639

IUPAC name: (*S*)-5-Methyl-2-methylthio-3-(4-nitrophenylamino)-5-phenyl-3,5-dihydroimidazol-4-one

CAS name: 4*H*-Imidazol-4-one, 3,5-dihydro-5-methyl-2-(methylthio)-3-[(4-nitrophenyl)amino)-5-phenyl-,(S)-

CAS #: N/A



RPA 221701

IUPAC name: (S)-5-Methyl-3-(2-nitrophenylamino)-5-phenylimidazolidine-2,4-dione
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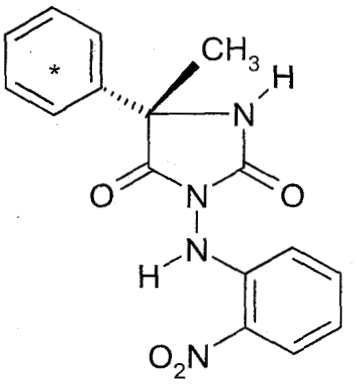
CAS #: N/A



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RPA 221607

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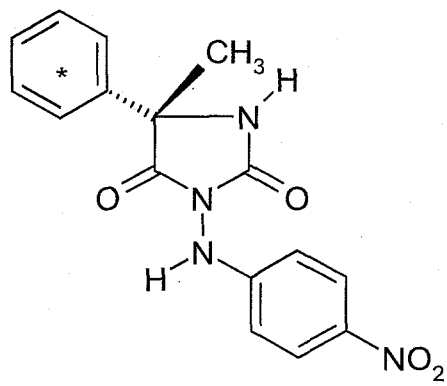
CAS #: N/A



*Position of [^{14}C]-radiolabel.

Attachment 2

Transformation Pathway Presented by Registrant

Figure 1 Proposed Degradation Pathway for Fenamidone in Soil under Aerobic Conditions

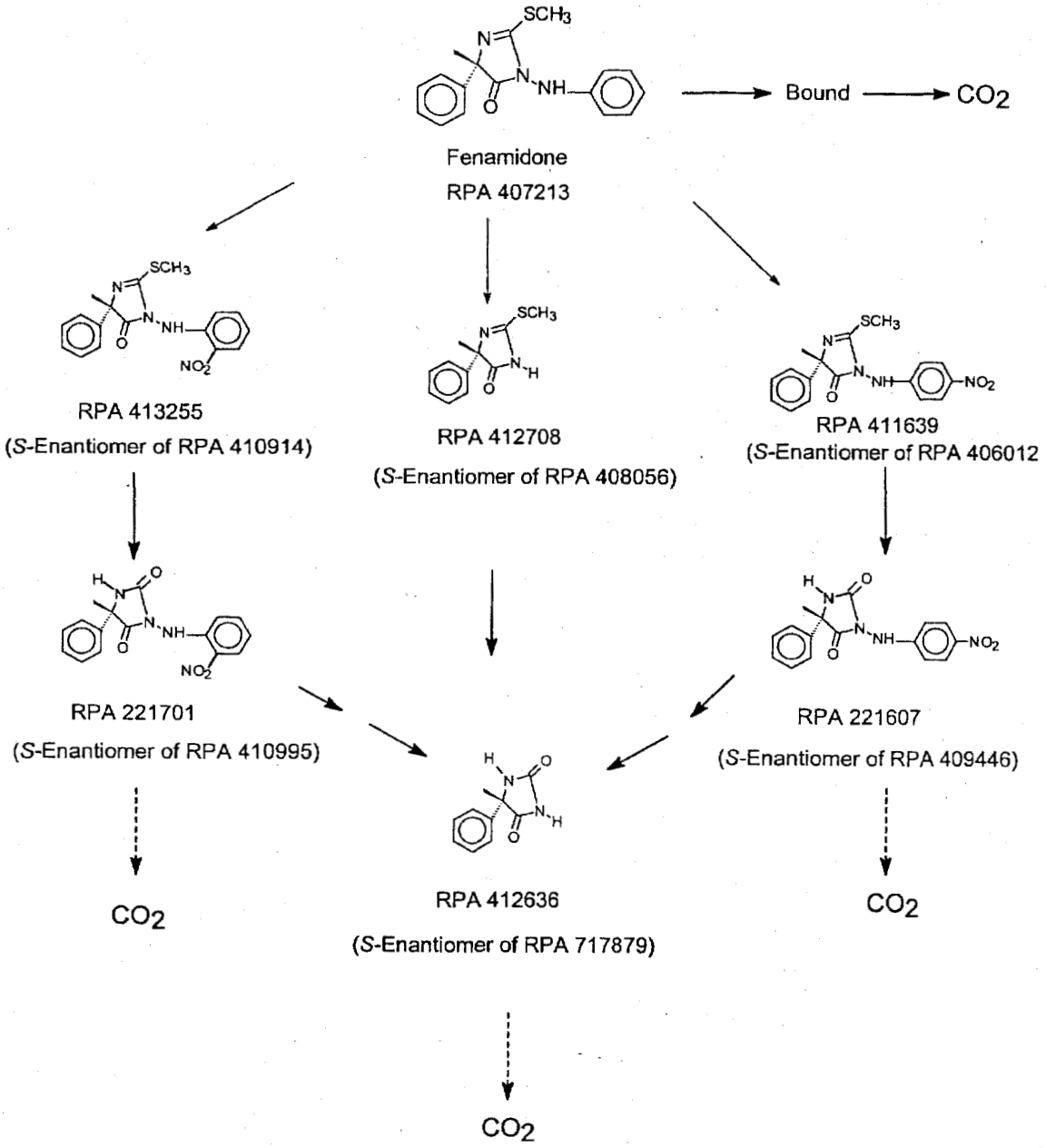
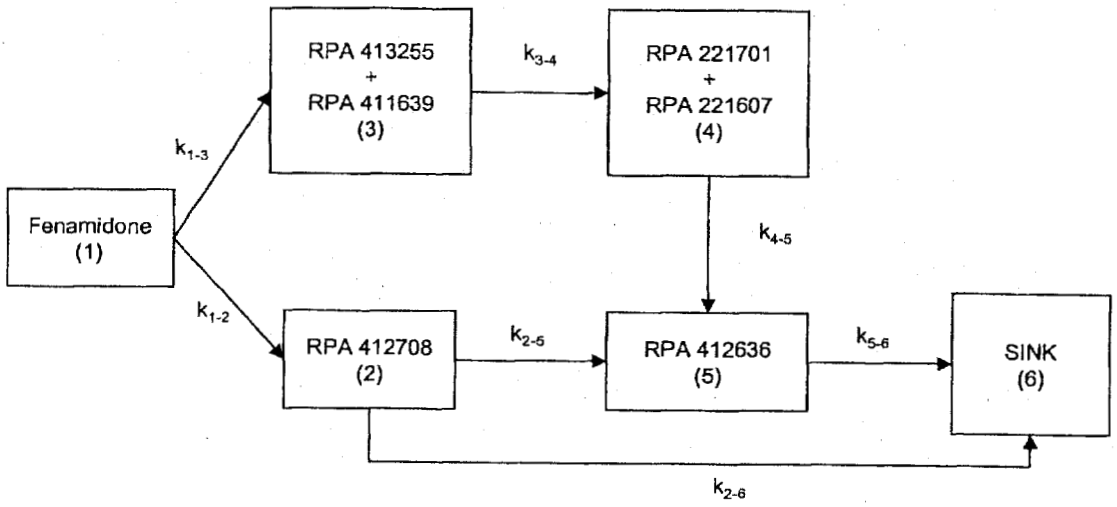


Figure 3 Kinetic Model for Degradation of Fenamidone in Soil under Aerobic Conditions

a) In Sandy Loam Soil



b) In Loam Soil